SUPPORTING INFORMATION

Structure-based Design of γ-Carboline Analogues as Potent and Specific BET Bromodomain Inhibitors
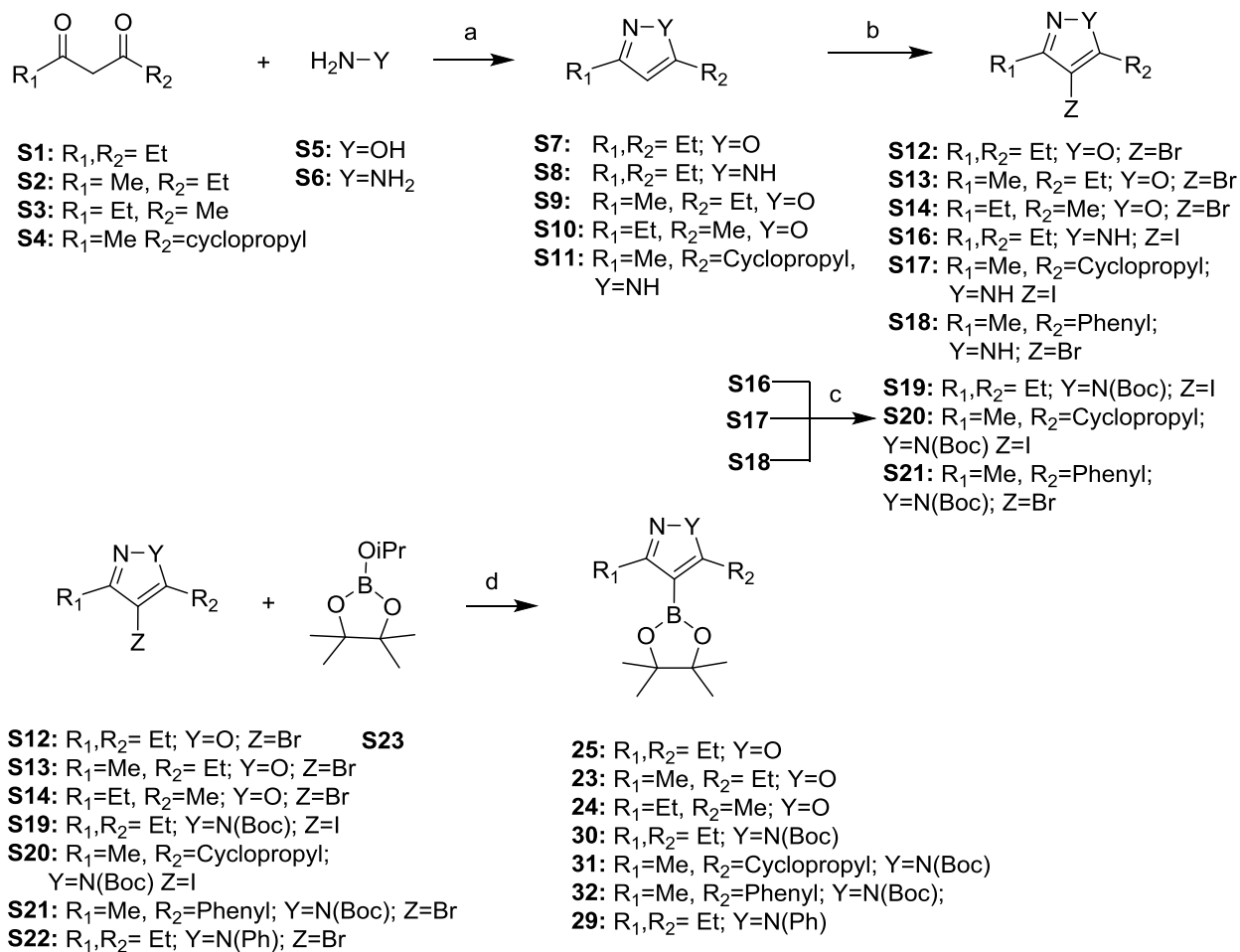
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Contents

Scheme S1 General synthetic method of five-membered hetereocylic boronate intermediates.

S1: R$_1$,R$_2$= Et   **S5:** Y=OH
S2: R$_1$= Me, R$_2$= Et   **S6:** Y=NH$_2$
S3: R$_1$= Et, R$_2$= Me
S4: R$_1$=Me R$_2$=cyclopropyl

S7: R$_1$,R$_2$= Et; Y=O
S8: R$_1$,R$_2$= Et; Y=NH
S9: R$_1$=Me, R$_2$= Et, Y=O
S10: R$_1$=Et, R$_2$=Me, Y=O
S11: R$_1$=Me, R$_2$=Cyclopropyl, Y=NH

S12: R$_1$,R$_2$= Et; Y=O; Z=Br
S13: R$_1$=Me, R$_2$= Et; Y=O; Z=Br
S14: R$_1$=Et, R$_2$=Me; Y=O; Z=Br
S16: R$_1$,R$_2$= Et; Y=NH; Z=I
S17: R$_1$=Me, R$_2$=Cyclopropyl; Y=NH Z=I
S18: R$_1$=Me, R$_2$=Phenyl; Y=NH; Z=Br

S16 ⎤
S17 ⎬ c
S18 ⎦

S19: R$_1$,R$_2$= Et; Y=N(Boc); Z=I
S20: R$_1$=Me, R$_2$=Cyclopropyl; Y=N(Boc) Z=I
S21: R$_1$=Me, R$_2$=Phenyl; Y=N(Boc); Z=Br

S12: R$_1$,R$_2$= Et; Y=O; Z=Br   **S23**
S13: R$_1$=Me, R$_2$= Et; Y=O; Z=Br
S14: R$_1$=Et, R$_2$=Me; Y=O; Z=Br
S19: R$_1$,R$_2$= Et; Y=N(Boc); Z=I
S20: R$_1$=Me, R$_2$=Cyclopropyl; Y=N(Boc) Z=I
S21: R$_1$=Me, R$_2$=Phenyl; Y=N(Boc); Z=Br
S22: R$_1$,R$_2$= Et; Y=N(Ph); Z=Br

25: R$_1$,R$_2$= Et; Y=O
23: R$_1$=Me, R$_2$= Et; Y=O
24: R$_1$=Et, R$_2$=Me; Y=O
30: R$_1$,R$_2$= Et; Y=N(Boc)
31: R$_1$=Me, R$_2$=Cyclopropyl; Y=N(Boc)
32: R$_1$=Me, R$_2$=Phenyl; Y=N(Boc);
29: R$_1$,R$_2$= Et; Y=N(Ph)

Reaction conditions: (a) EtOH or MeOH/H$_2$O, reflux; (b) NBS or NIS, DMF, overnight; THF (c) (Boc)$_2$O, DMAP, 0 ^{o}C to rt; (d) BuLi, THF, -78 ^{o}C.

Figure S1. Chemical structure of Fluorescence-labeled BET inhibitor used in our fluorescence Polarization assays for BDR2-BDR4 BD1 and BD2 domain proteins.
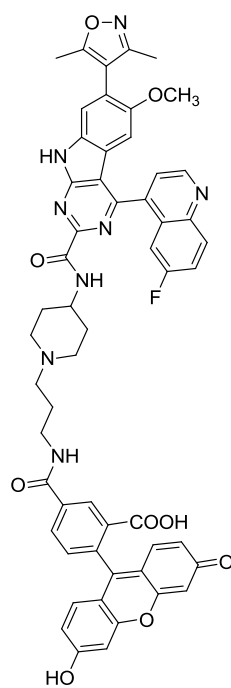
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Table S1: X-ray Crystallography Data Collection and Refinement Statistics

Data Collection	BRD4 BD2- compound **18**
PDB ID	4Z93
SpaceGroup	$P2_12_12$
Unit Cell a, b, c (Å)	51.862, 72.696, 32.115
Wavelength (Å)	1.07820
Resolution (Å)[1]	1.27 (1.29-1.27)
Rsym (%)[2]	4.5 (32.6)
$<I/sI>$[3]	20 (5)
Completeness (%)[4]	98.9 (96.7)
Redundancy	6.2 (6.1)
Refinement	
Resolution (Å)	1.27
R-Factor (%)[5]	15.6
Rfree (%)[6]	18.5
Protein atoms	1776
Water Molecules	119
Unique Reflections	32482
R.m.s.d.[7]	
Bonds	0.010
Angles	0.98
MolProbity Score	0.50
Clash Score	0
Z-Score[8]	-0.16
RSCC (%)[8]	93.8
RSRV (%)[8]	10.2

[1]Statistics for highest resolution bin of reflections in parentheses.

[2]$R_{sym} = \Sigma_h\Sigma_j \, |\, I_{hj} - <I_h> \, | \, / \Sigma_h\Sigma_j I_{hj}$, where I_{hj} is the intensity of observation j of reflection h and $<I_h>$ is the mean intensity for multiply recorded reflections.

[3]Intensity signal-to-noise ratio.

[4]Completeness of the unique diffraction data.

[5]R-factor = $\Sigma_h \, |\, |F_o| - |F_c| \,|\, / \Sigma_h |F_o|$, where F_o and F_c are the observed and calculated structure factor amplitudes for reflection h.

[6]R_{free} is calculated against a 5% random sampling of the reflections that were removed before structure refinement.

[7]Root mean square deviation of bond lengths and bond angles.

[8]Values calculated using the Predeposition Electron-Density Server.